DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region M3892N

Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

Telephone (973) 526-6008

WARNING LETTER

Certified Mail
Return Receipt Requested

File # 00-NWJ-35

June 27, 2000

Bernard J. Kelley
President
Merck Manufacturing Division
1 Merck Drive
P.O. Box 100
Whitehouse Station, NJ 08889

Dear Mr. Kelley:

During our February 1 through March 16, 2000 inspection of your manufacturing facility located at 126 East Lincoln Avenue, Rahway, New Jersey, our investigator documented deviations from current good manufacturing practices applied to the manufacture of Active Pharmaceutical Ingredients (API's). These deviations cause your drugs for human use to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act. The deviations included:

- Use of a batch of intermediate material rejected due to contamination with a foreign substance in manufacturing two Amitriptyline finished API lots (ERF5390 and ERF5411). As of the date of the inspection, portions of both lots remain under your direct control and approved for distribution.

- Out-of-specification data were averaged with passing data to facilitate the release of Dorzolamide HCl Pure lot HRDT090, Dorzolamide HCl Crude lot HRDR090, and Impenem non-sterile lots HRIC460 and HRIB610. In addition, for each lot an average of several test results was reported without mention of the result being an average of multiple test results.

- Out-of-specification assay results for lot HRVF030 of Rofecoxib Pure were invalidated on the premise that a sampling error had occurred. No documentation or data was presented or discovered during the inspection to support that conclusion. This lot was repeatedly tested (6 times) and the third through sixth re-tests also gave out-of-specification results. The third

and fourth re-tests were invalidated due to sample preparation. Again there was no evidence of sample preparation error and the procedure is not defined in the analytical method.

- Re-sampling and re-testing was performed on intermediate API lots without justification for: [redacted] pre-reaction solution for Amitriptyline lots HRAR210A, 210B, 220A, 260A, and 280A for water content failures using Karl Fischer determination; Rofecoxib Pure lots HRVD690, HRVF650, HRVD460, HRVF190 and HRVF200 for extraneous matter failures; Rofecoxib Pure lot HRVD240 for a degradation peak; and ten Bromosulfone (starting material for Rofecoxib) lots for elevated impurity levels.

- Two lots of Rofecoxib Pure (HRVF770 and HRVF850) were released for distribution despite analytical findings that they were contaminated with polypropylene fibers in excess of the action limit. Six lots of Rofecoxib Pure also demonstrated polypropylene fiber contamination but were deemed acceptable and released. Twenty-three lots of Rofecoxib pure were subjected to the same sifting process, later identified as the cause of the polypropylene contamination. The sampling procedure was inadequate, as it did not include an acceptable number of drums to be sampled. Also, the extraneous material action limit used in this investigation is inadequate, in that no instructions are present if extraneous material in excess of the specification limits is found.

- Manufacturing investigations for nine Imipenem batches were not completed timely, ranging from ten months' duration to as long as two years.

The above deviations are not intended to be an all-inclusive list of violations. As a manufacturer of drug products for human use, you are responsible for assuring that your overall operation and the products you manufacture are in compliance with the law. It is your responsibility to assure adherence with Current Good Manufacturing Practices. Federal agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts. Additionally, pending Antibiotic Form 6, New Drug Applications, Abbreviated New Drug Applications, or export approval requests may not be approved until the above violations are corrected.

We acknowledge receipt of your corrective actions proposed on April 5, 2000. Our initial review indicates those corrections should be adequate to correct the deviations. However, if the corrections do not prevent the reoccurrence of violations, or if new, significant violations surface, the Agency may undertake in regulatory action without further notice such as seizure and /or injunction.

You should notify this office in writing, within 15 working days upon receipt of this letter, of any further steps you have taken to bring your firm into compliance with the law. Your response should include each step being taken, that has been taken, or will be taken to correct the violations and prevent their recurrence. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time frame within the corrections will be completed. Please include copies of any available documentation demonstrating that corrections have been made.

Your reply should be directed to Kirk D. Sooter, Compliance Officer, U.S. Food and Drug Administration, 10 Waterview Boulevard, Third Floor, Parsippany, New Jersey 07054. If you have any questions about this letter, please contact Mr. Sooter at 973-526-6008.

Sincerely yours,

Douglas I. Ellsworth
District Director